REMARKS

In regard to the amendment to claim 3, the limitation from claim 4 has been incorporated into the claim and claim 4 has been cancelled.

Support for the term "cells stably expressing" in claims 24 and 25 is on page 17, lines 10-19.

Support for the recitation of "ischemia-reperfusion injury" in claims 26 and 28 is found on page 8, lines 17-19; page 11, lines 11-16; page 28, lines 1-12; Example 16 and Figure 14.

Support for claim 31 is on page 28, lines 27-31; page 43, lines 27-34; page 44, lines 1-3.

Support for claim 35 is on page 25, lines 3-13.

Support for new claim 36 is on page 31, lines 6-14.

Support for new claims 37 and 38 is on page 17, lines 10-19.

Support for new claim 39 is on page 28, lines 1-12; page 72, lines 19-24.

35 U.S.C. §112, First Paragraph Rejection

The specification was objected to and claims 3-5, 10-18 and 26-33 (page 5, 4th paragraph) were rejected under 35 U.S.C. §112, first paragraph and another rejection under 35 U.S.C. §112, first paragraph of claims 1-6 and 8-34 (page 7, #21) as failing to provide an adequate written description of the invention, failing to adequately teach how to make and/use the invention and failing to present the best mode.

As Applicant pointed out in the response filed November 29, 1994, there are three separate and distinct requirements under 35 U.S.C. §112, first paragraph. Our interpretation of the Examiner's arguments is that the only basis of the objection and rejection under §112,

first paragraph is under enablement requirement of this section and not to the written description or best mode requirement. Thus, Applicant's reply is directed to the enablement requirement under §112, first paragraph. Applicant also questions why some claims have been "doubly" rejected under §112, first paragraph as this seems to be a rather unusual practice.

In the office action dated June 1, 1994 (Paper 8) the Examiner rejected claims 3-5, 10-18, 21-23 and 26-33 under 35 U.S.C. §101 as inoperative and as such lack utility. In the next office action dated March 7, 1995 (Paper 12) the Examiner has withdrawn the rejection under §101. The Examiner now rejects the same claims under §112, first paragraph and has made arguments identical to those put forth as the basis of rejection under §101.

Applicant submits that the subject matter of the rejected claims encompass not only methods of treatment but also antibodies, pharmaceutical compositions using the antibodies, methods of diagnosis and methods of making antibodies.

To satisfy the enablement requirement under §112, first paragraph, the specification must teach how to make and use the claimed subject matter.

In terms of the claims directed to the hybridoma, i.e. claim 6, and claims directed to the antibodies, i.e. claims 1, 2, 19-24 and 34, Applicant need only enable the making of the hybridoma and antibodies and a use of the hybridoma and antibodies. The specification clearly teaches one skilled in the art the immunogen, the method of immunization, the method of making the hybridoma and monoclonals and the method for screening the culture supernant of the hybridoma for the antibodies of the present invention. Further, the specification teaches numerous uses of the antibodies both as diagnostic agents as well as therapeutic agents. The

specification teaches the use of the antibodies in detecting both E- and L-selectin bearing cells. This use in and of itself is sufficient to satisfy the enablement requirement for the claimed hybridoma and antibodies. The product, i.e. hybridoma or antibodies, whether the product is used in vitro or in vivo, is still the same product.

The Examiner states that Applicant has not provided evidence for another common epitope shared between E- and L-selectin other than that recognized by EL-246. Moreover, the Examiner is requesting that the claims be limited to the working example, i.e. EL-246. Applicant respectfully submits that this is contrary to the holding of In re Wands, 858 F.2d 731, 735-736, 8 USPQ 2d 1400, 1402-1403 (Fed. Cir. 1988); In re Vaeck, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991); Ex parte Obukowicz, 27 USPQ 2d 1063 (Bd. Pat. App. and Inter. 1992). Applicant submits that the present invention is a pioneering invention and should be afforded a broad scope of protection. Applicant is the first to recognize that different selectins share common epitopes. The art, prior to Applicant's invention focused totally on selectin antibody unique for each of the different selectins. One skilled in the art, advised of Applicants invention of antibodies recognizing two different selectin, can use the teachings of the specification to select for other antibodies that recognize an epitope common to both E-selectin and L-selectin. These antibodies at the very least would be expected to be useful diagnostic agents to detect E-selectin and L-selectin bearing cells thus satisfying the enablement requirement under §112 for the claims directed to antibodies. Applicant does not have a burden under §112, first paragraph of providing evidence that all antibodies falling within the scope of the claimed antibodies are "powerful inhibitor(s) of multiple cell-cell interactions" as he suggests. The

demonstration that the antibodies are useful in diagnosis or detection of cell types is sufficient to satisfy the enablement requirement. The Examiner seems to be applying an unrealistically low level of skill in the art under §112, first paragraph, particularly an inability to deal with the need to undertake reasonable experimentation and screening. Applicant submits that the teachings of the specification fully enable one skilled in the art to make and screen for the antibody as claimed without undue experimentation.

Claim 8 and new claim 35 are directed to a method of detecting E-selectin and L-selectin bearing cells in a biological sample. This is a diagnostic method for identifying cell types. The specification clearly enables a method of detecting cells using immunoassays and the antibody of the present invention (page 25, lines 4-34; page 26; page 27, lines 1-14; Example 10). Certainly one skilled in the art would have no problem applying the teachings of the specification in the practice of the claimed method. Those in the art could readily practice the method in vitro, in situ, or in vivo without undue experimentation.

Claim 25 and new claim 36 are directed to a method of producing antibodies using as the immunogen cells stably expressing a selectin. The specification specifically exemplifies a method of making the antibodies using such an immunogen. Those skilled in the art, armed with the specification that teaches the immunogen as well as the methods of screening, will select for an antibody capable of binding a common antigenic determinant on E-selectin and L-selectin.

The remainder of the rejected claims, i.e. claims 3-5, 10-17 and 26-33 relate to methods of treatment. Claims 4, 9 and 17 have been cancelled without prejudice to advance prosecution and in no way should be construed that such claims are not enabled by the teachings of the

specification. On the contrary, Applicant submits that the subject matter, including the method of treatment claims are fully enabled by the teachings of the specification.

In claims 10, 26, 30 and 32 the recitation of "prevent" has been deleted, without prejudice. While it is desirable that the claimed methods "prevent", it is certainly not mandatory that the method achieve prevention in order for the method to be effective for each of the recited purposes. In making this amendment, it should in no way be construed that the methods do not "prevent" a particular function or response. The Examiner has implied that for enablement the methods must be 100% effective for all possible indications. Applicant contends that the methods need not be 100% effective to meet the enablement requirement, but need only achieve an effective amount of inhibition. The specification clearly discloses the inhibition of leukocytes and endothelial cells under in vitro, in situ, and in vivo.

The Examiner states that Applicant has not disclosed how to use the antibodies therapeutically in humans. Many of the reasons put forth by the Examiner, have been addressed by Applicant in his previous response of November 29, 1994. Moreover, the specification provides specific inflammatory conditions to be treated using the antibody, or fragments thereof (p. 27, lines 20-34; p. 28, lines 1-34; p. 29, lines 1-4); it provides specific doses to be used in treatment (p. 30, lines 26-29; page 71, lines 27-29); it provides specific treatment regimes (p. 31, lines 15-28); it provides specific routes of administration (p. 31, lines 29-34); it provides specific formulations (p. 32, lines 3-34; p. 33; p. 34, lines 1-16); and it provides an in vivo 1/2 life of the antibody (p. 73, lines 15-19).

There is no patent rule or court decision that states that human clinical data is required to show enablement for a method of treatment. Applicant's disclosure along with the specific in vitro and in vivo data using animal models is sufficient to establish a therapeutic use in humans (In re Brana, 51 F.3d, 1560). The disclosure of these parameters would allow one of ordinary skill in the art to practice the claimed method of treatments in humans without undue experimentation.

The purpose of treating inflammation with antibodies does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. In re Jolles, 628 F.2d at 1327, 206 USPQ at 890. The prior art has identified antibodies successful as immunotherapeutics such as anti-inflammatory or anti-adhesion agents. As Applicant has previously pointed out the mouse monoclonal antibody, OKT3, has been shown to be clinically effective in preventing renal allograft rejection. In addition to OKT3 other non-human antibodies which have been used in humans. A few examples include: Digibind, a sheep polyclonal antibody fragment used as standard therapy for life-threatening digitalis toxicosis in humans (Exhibit A - Antman, E.M. et al 1990 Circulation Vol. 81:1744-52); Myoscint, an indium-111-labeled mouse antibody that images myocardial necrosis in humans (Exhibit B - Johnson, L.L. et al 1989 J. Am. Coll. Cardiol. Vol. 13:27-35); and 7E3, a mouse anti-platelet antibody that binds to the platelet surface receptor for fibrinogen and inhibits platelet function (Exhibit C - Coller, B.S. et al 1983 J. Clin. Invest. 72:325-8). Thus sheep and mouse antibody based immunotherapeutics which were known in the art have been demonstrated to reach the intended target tissue and function for their intended purpose.

7E3, like the antibody of the present invention, is an anti-adhesion based therapeutic. C7E3 Fab (tradename ReoPro), a chimeric antibody of 7E3, has been approved by the FDA for treatment of patients undergoing percutaneous transluminal coronary angioplasty who are at high risk for abrupt vascular closure. The efficacy of the 7E3 antibody in humans was predicated on in vitro and in vivo studies using animal models. In 1985, Coller, B.S. et al reported inhibition of dog platelet function by in vivo infusion of $F(ab')_2$ fragments of 7E3 (Exhibit D - Coller, B.S. et al 1985 Blood Vol. 66 No. 6:1456-1459).

Thus, one skilled in the art was aware that antibodies based immunotherapies were known in the art and that their clinical utility in humans was predicated on successful studies in vivo using animal models. Applicant submits that based on the in vitro and in vivo animal studies disclosed for the present invention that those skilled in the art would not have doubted the utility of the present invention of treating inflammatory diseases in humans. Even if one skilled in the art would have reasonably questioned the asserted utility, Applicant has provided sufficient evidence to convince one skilled in the art of the asserted utility. In particular, Applicant has provided a declaration by Dr. Steinberg filed November 29, 1994. This declaration provides in vivo test results in an animal model of an antibody within the scope of the claims. The results unequivocally showed that treatment using the antibody of the present invention prevented mortality from lung ischemia/reperfusion injury in the animal model. Moreover, this dramatic effect of treatment occurred using one dose. Dr. Steinberg, as a clinician skilled in the art of treating transplantation patients, declared that the efficacy of the EL-246 antibody, as demonstrated by the sheep lung ischemia/reperfusion model is reasonably predictive of efficacy

of the EL-246 antibody in humans for treatment of inflammatory-induced injury that occurs in lung transplantation and pulmonary injuries (Steinberg Declaration, #17). Such evidence alone should be sufficient for enablement (In re Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995).

The Examiner contends that the Steinberg declaration is insufficient to overcome the rejection of claims 3-5, 10-18 and 26-33 under 35 U.S.C. §112, first paragraph. The Examiner must be reminded that he must treat as the true credible statements made by a declarant in a declaration provided under 37 C.F.R. §1.132. The PTO guideline for examination of applications has made it clear that not accepting the opinion of a qualified expert that is based on a appropriate factual record is clearly improper (Federal Register Vol. 60, No. 135, p. 36265, 1995).

The Examiner's factually unsupported reasoning for deciding that the Steinberg declaration was insufficient is that in the method of treatment in the lung ischemia/reperfusion animal model the antibody was administer prior to reperfusion. He further states "In the instant application, antibody treatment occurred before the stimulus of the inflammatory response, therefore it is not clear that antibody treatment would be effective under normal clinical conditions". Applicant notes that "normal clinical conditions" have not been elucidated by the Examiner.

It appears that the Examiner has misinterpreted the teachings of the specification and the Steinberg declaration and attached exhibits concerning ischemia/reperfusion injury. In the sheep lung ischemia/reperfusion mode the inflammatory event is initiated by the ischemia, not the reperfusion (see Steinberg, #6). The ischemia in the animal model is induced by occlusion of

the left main pulmonary artery for 3 hours (Steinberg, J. Heart Lung Transp. Vol 13, p. 307, 2nd column, lines 26-28). The antibody of the present invention was administered after the 3 hour occlusion of the pulmonary artery and ten minutes prior to reperfusion (Steinberg, J. Heart Lung Transp. Vol. 13, p. 307, 2nd column, lines 30-36). Therefore the antibody was administered after the initiation of the inflammatory events. As pointed out in the Steinberg declaration, lung transplantation and pulmonary injuries result in the initiation of inflammatory events in humans (#7). Moreover, Dr. Steinberg opines that the inflammation-induced injury that occurs in the lung ischemia/reperfusion animal model corresponds with the inflammation-induced injury that occurs in lung transplantation and pulmonary injuries in humans (#8). As in the case of human lung transplantation, the pulmonary arteries leading to one or both lungs are clamped off resulting in ischemia that initiates an inflammatory event. The trauma of cutting the arteries to remove the lung leads to further inflammation. The physician may administer the antibody of the present invention at any appropriate time to prevent or inhibit blockage of the arteries leading to the new lung. Thus, the animal model and method of treatment is entirely consistent with what occurs in humans. Applicant respectfully submits that the Examiner has failed to meet his burden of showing that one skilled in the art would have a rational scientific basis for doubting the truth of the statements in the specification or in the Steinberg declaration for concluding that the specification is not enabling to those skilled in the art for practicing the invention.

The Examiner is impermissibly requesting human clinical studies to satisfy enablement under the meaning of §112, first paragraph. Human clinical studies is not a prerequisite for

finding a compound useful within the meaning of the patent laws. (Federal Register, Vol. 60, No. 135, 36263-36265, 1995, Cross v. Iizuka, 224 USPQ at 742; Scott 34 F.3d 1058, 1063, 32 USPQ 2d 115, 1120; In re Brana, 51 F.3d 1560).

In support of the Examiner's rejection under §112, first paragraph he has impermissible pointed to a negative statement from articles that in general advocate the use of antibodies in methods of treatment. Certainly all methods of treatment have some limitations and may have side effects. However, these articles do not support the Examiner's view that the specification does not enable methods of treatment. Moreover, issues relating to side effects of a method of treatment are matters for the FDA to address and not the Patent Office. (In re Brana, 51 F.3d at 1568, 34 U.S.P.Q. 2d at 1442, citing Scott v. Finney, 34 F.3d at 1063, 32 U.S.P.Q. 2d at 1120).

For instance, the Examiner cites Bargatze (1994) because of a statement that says the effectiveness of EL-246 in vivo will come from studies in which antibody is injected into animals and the effect on either lymphocyte recirculation or inflammation evaluated. Applicant contends that this statement provides evidence that the present specification is enabling as the specification teaches how to inject the antibody into animals, it teaches how to measure lymphocyte recirculation and it teaches how to evaluate inflammation.

In regard to Mountain et al, Applicant notes that he was provided only with selected portions of this article. In view of the title of the article, Applicant must assume that the overall gist of the reference is that antibodies may be used in methods of treating diseases. As the first

page states, "MAbs have already been used clinically for the diagnosis and therapy of several human disorders, notably cancer and infectious diseases and for modulation of immune response.

Shaffer was cited for a statement that treatments using monoclonal antibodies are promising but involve toxicities. The author provides no data to support the statement, but in any event, toxicities or other side effects is not a patent issue but an issue for the FDA.

The whole article of Waldmann (1991) concerns using monoclonal antibodies in vivo for diagnosis and therapy. It does not advocate that methods of treatment never work or that they should be abandoned.

Jolliffe confirms Applicant's previous statements that OKT3 is effective in methods of treating allograft rejection.

Steinberg teaches that EL-246 recipients had an unequivocal physiologic advantage compared to animals not treated with EL-246. The statements in Steinberg et al that the Examiner refers to do not relate to the efficacy of EL-246 but relate to the researchers inability to dissect the role of E- and L-selectin in the ischemic injury.

Applicant submits that the specification fully enables one skilled in the art to practice the invention of pending claims 1, 2, 3, 5, 6, 10-16, 19-24, 26-33, 34 and new claims 35-39. Reconsideration and withdrawal of the rejections under §112, first paragraph is respectfully requested.

35 U.S.C. §112, Second Paragraph

Claims 30-31 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The office action states that the recitation of "endothelial cell layer" is indefinite and argues that "endothelial cell layer" implies in vitro use as compared to in vivo use. Moreover, the Examiner states that the claims are limited to in vivo use.

Applicant would first like to point out that claim 30 has no recitation in it which limits the method to in vivo treatment only. Nor does Applicant believe that there is any justification to limit claim 30 to in vivo under §112, second paragraph as the method may be applied in vitro as well as in vivo. Thus, Applicant maintains that "endothelial cell layer" is an appropriate term to refer to both in vitro and in vivo. Claim 31 by the recitation of "lymphatic vessel, artery, vein, or postcapillary venules" implies a limitation to in vivo or ex vivo treatment. Thus, it has been amended to recite "endothelium".

Reconsideration and withdrawal of the rejection is respectfully requested.

35 U.S.C. §103 Rejection

Claims 1-34 were rejected under 35 U.S.C. §103 as being unpatentable over Kishimoto et al PNAS, 1990 in view of Lasky et al (U.S. Pat. No. 5,098,833), Bevilacqua et al (U.S. Pat. No. 5,081,034) and Watson et al (Nature, 1991). The rejection now applies to claims 1-3, 5-8, 10-16, and 18-34 as claims 4, 9 and 17 were cancelled herein without prejudice.

The present invention are antibodies that have dual specificity for E-selectin on endothelial cells and L-selectin on leukocytes. The present invention also encompasses methods of making the antibodies, methods of using the antibodies as well as pharmaceutical compositions containing the antibodies.

Before obviousness may be established, the Examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles (Ex parte Kranz 19 U.S.P.Q. 2d 1216, 1218).

The Examiner's rational for rejecting all the claims, be they antibody claims, methods of diagnosis, or methods of treatment appears to be that the motivation for arriving at the present invention comes from a desire in the art to have methods of treating inflammatory diseases. This certainly was a desirable goal in the art, however, it ignores the specific teachings of the cited art.

Kishimoto et al PNAS is directed to specific antibodies for L-selectin found on leukocytes. Lasky et al is directed to L-selectin and briefly mentions L-selectin specific antibodies. Bevilacqua et al is directed to E-selectin, which is found on endothelial cells, and E-selectin specific antibodies. Watson Nature is mainly directed to derivatives of L-selectin.

None of these citations, alone or in combination, teach or suggest the remotest possibility that one antibody could be produced having specificity for both E-selectin on leukocytes and L-selectin on endothelial cells. Those skilled in the art would have viewed such an idea with skepticism as those in the art knew that antibodies by their very nature are exquisitely specific in their recognition. Those in the art would not have predicted that an antibody could be raised

having dual specificity to both E-selectin and L-selectin which are on different cell types in the same species and that this same antibody would also recognize E- and L-selectin from different species of mammals. Moreover, all the antibodies of the prior art were shown to be specific for one or the other selectin, but not both E-selectin and L-selectin.

Therefore, the art fails to provide the requisite motivation to one in the art to attempt to produce the antibodies of the present invention, let alone provide a likelihood of success.

The Examiner agrees with Applicant in that Kishimoto et al PNAS does not teach making an antibody that binds a common E-/L-selectin epitope (Paper 12, #27). Kishimoto et al PNAS only discloses L-selectin specific antibodies.

Kishimoto et al PNAS fails to provide any motivation or raise the slightest possibility that antibodies could be raised that would recognize a common epitope on both E-selectin and L-selectin, as disclosed and claimed in the present invention.

The Examiner stated that the immunogens and the antibody screening procedures of the cited references are the same as the instant invention (Paper 12, #27, p.10).

Applicant has filed along with this response, a §1.132 declaration by Mark A Jutila which clearly and unambiguously points out that the immunogen, method of immunization and initial screening procedures and resulting antibodies of the present invention are different from those of Kishimoto et al PNAS.

Kishimoto et al PNAS discloses the use of a shed form of L-selectin as the immunogen to elicit the disclosed DREG antibodies. The method of immunization disclosed in Kishimoto et al PNAS required adoptive transfer of immune spleen cells into syngeneic animals. The initial

screening taught by Kishimoto et al PNAS was designed to select for antibodies specific for the shed form of L-selectin.

In sharp contrast to Kishimoto et al PNAS, Applicant does not teach or suggest a shed form of L-selectin as the immunogen. The method of immunization of the present invention does not require an adoptive transfer into syngeneic animals. The initial screening taught by Applicant uses E-selectin transfected L1-2 cells to select for positive clones (page 35, lines 2-4).

The antibodies of the present invention are novel and nonobvious over those disclosed by Kishimoto et al as detailed in Table 1 of the §1.132 declaration of Dr. Jutila. The antibodies of the present invention bind to E-selectin an endothelial cells and E-selectin transfectants and L-selectin on leukocytes and L-selectin on L-selectin transfectants. Of critical importance is the fact that the antibodies of the present invention do not react with the shed L-selectin immunogen taught by Kishimoto et al PNAS. The §1.132 declaration of Takashi K. Kishimoto, attached herein, provides a factual showing that the EL-246 antibody of the present invention failed to bind to shed L-selectin. Both Dr. Jutila and Dr. Kishimoto declare in their respective §1.132 declarations that the immunogen of Kishimoto et al PNAS would fail to elicit antibodies of the present invention. In fact, as pointed out in the §1.132 declaration of Dr. Jutila, Dr. Jutila failed to produce antibodies of the present invention using the immunogen, method of immunization and initial screening as taught by Kishimoto et al PNAS.

The vast differences between the antibody of the present invention and the DREG antibodies disclosed in Kishimoto et al PNAS are so significant and unexpected that they weigh more heavily than the few similarities between the claimed antibodies and those of the prior art.

The differences between the antibodies of the present invention and the DREG-56 antibody is of practical significance. The antibody of the present invention blocks both E-selectin mediated functions and L-selectin mediated function. The DREG-56 antibody blocks only L-selectin mediated functions. The most dramatic difference having practical significance is the demonstration that EL-246 antibody protected 100% of sheep from death due to lung ischemia/reperfusion injury, whereas treatment using the DREG-56 antibody was no better than saline in protecting sheep (33% protection).

Applicant has met his burden of submitting objective, factual evidence to establish differences and nonobvious of the antibodies of the present invention and have shown that these antibodies are unexpected, unobvious and are of practical significance sufficient to overcome the obviousness rejection (Ex parte C 27 U.S.P.Q. 2d 1492, 1497; Ex parte Phillips 28 U.S.P.Q. 2d 1302, 1303 (Bd. Pat. App. and Int. 1993)).

Lasky et al, Bevilacqua et al and Watson et al fail to overcome the deficiencies of Kishimoto et al. Lasky is directed to L-selectin specific antibodies only. Bevilacqua et al is directed to E-selectin specific antibodies only. Watson is mainly directed to derivatives of L-selectin. None of these references provide the requisite motivation to one skilled in the art to make an antibody specific for both E- and L-selectin, as no such antibody have previously been reported or suggested in the art. Thus, the antibodies of the present invention are nonobvious in view of the prior art antibodies.

That prior art products of L-selectin specific antibody or E-selectin specific antibody which were disclosed as useful in treating inflammation, they have no bearing on the methods of treatment of the present invention.

The present invention uses a hitherto unknown and nonobvious product, i.e. antibody having recognition for both E-selectin and L-selectin, for the treatment of inflammation. Claims 3, 5, 8, 10-16, 26-33 and 35 are methods of using the novel and nonobvious antibodies and are patentable as "process of using" under In re Pleuddemann 910 F.2d 823, 15 U.S.P.Q. 2D 1738 (Fed. Cir. 1990) and In re Mancy, 499 F.2d 1289, 182 U.S.P.Q. 303 (CCPA 1974).

Applicant submits that claims 1-3, 5-8, 10-16, 18-34 and new claims 35-39 are in condition for allowance. Favorable action by the Examiner is earnestly solicited.

Respectfully submitted,

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